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4722201

From: STIC-EIC1700
Sent: Tuesday, November 18, 2003 7:57 AM
To: STIC-ILL
Subject: FW: 10014270

-----Original Message-----
Fr m: Gakh, Yelena
Sent: Monday, November 17, 2003 8:16 PM
To: STIC-EIC1700
Subject: 10014270

Dear Kendra,

please submit the following:

TITLE: Evaluation of the rainbow dynamic dissolution monitor semi-automatic fiber optic dissolution tester
AUTHOR(S): Schatz, Caspar; Ulmschneider, Michel; Altermatt, Rolf; Marrer, Stephan
CORPORATE SOURCE: Pharmaceutical Quality Assurance and Quality Control, F. Hoffmann-La Roche Ltd., Basel, Switz.
SOURCE: Dissolution Technologies (2000), 7(4), 8, 10-12, 14, 16-17

Thanks,

yelena

Yelena G. Gakh, Ph.D.

Patent Examiner
USPTO, cp3/7B-08
(703)306-5906

BHL ordered 10
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Evaluation of the Rainbow Dynamic Dissolution Monitor™ Semi-automatic Fiber Optic Dissolution Tester

Caspar Schatz, Michel Ulmschneider, Rolf Altermatt, Stephan Marrer
Pharmaceutical Quality Assurance and Quality Control, F. Hoffmann-La Roche Ltd, Basel, Switzerland
email:caspar.schatz@roche.com

Summary

The Rainbow Dynamic Dissolution Monitor™ (Delphian Technology LP, Ardsley, USA) is a simple and convenient UV absorbance technique for acquiring precise, accurate, reproducible and robust dissolution profiles of drug formulations containing a single active ingredient. The instrument and its software are GMP compliant. Benefit analysis shows that it has significant advantages for dissolution over systems using filtering and flow -through cells. The Rainbow Dynamic Dissolution Monitor™ is thus suitabl for routine dissolution analysis in pharmaceutical quality control.

Introduction

The Rainbow Dynamic Dissolution Monitor™ uses 12 fiber optic immersion probes residing in vessels of two dissolution baths throughout the dissolution test. Two deuterium lamps are used as a light source. After interacting with the sample, the light is guided to a series of 12 photo diode array ultraviolet monolithic miniature spectrometers (UV MMS, Carl Zeiss, Jena, Germany) [1] which measure from 200 to 400 nm with an absolute wavelength accuracy of 0.2 nm and a temperature drift less than 0.005 nm/K. The spectral pixel spacing is 0.8 nm, giving a Rayleigh resolution of about 3 nm. Stray light measured at 240 nm using a deuterium lamp and potassium iodide solution (10 g/L) is 0.3 % [2]. Each spectrometer unit and its probe are referred to as a channel.

Before performing a dissolution run, the system collects 0% and 100 % transmission blanks and standard absorbance scans per channel. Hence the amount of dissolved active compound is determined with a single point calibration. To eliminate standard preparation errors, a second quality control standard is measured for control purposes only. During a run, the system can acquire absorbance scans every 10 seconds. The software incorporates two methods to correct for turbidity and scattering effects. The first method uses two wavelengths: one to determine the active compound, the other to act as a compensation wavelength. The second method is based on a second derivative algorithm using a wavelength range [1]. It uses a very simple algorithm to estimate th second derivative and a form of co-addition of several wavelengths to improve the signal to noise ratio.

Experimental

All the experiments were performed using the Rainbow Dynamic Dissolution Monitor™ with 10 mm pathlength Hellma ultra mini-immersion probes, (type 661.673-UV, Hellma GmbH & Co., Müllheim/Baden, Germany) to acquire UV measurements. Only six channels/probes were evaluated, always using one scan per measurement in each case.

System suitability

Suitability was assessed in terms of fiber optic unit transmission and the linear range of the spectroscopic assembly.

Transmission

The relative energy of 100% transmission spectra of artificial intestinal fluid pH 7.5 (reference Anticoagulant Tablets Section, page 10, for fluid composition) was plotted against wavelength as a measure of channel and probe transmission.

Linear range

The linear range of all six evaluated channels was tested using a dilution series of potassium dichromate (spectroscopy grade, Fluka Chemie AG, Buchs, Switzerland) in 0.01 N sulfuric acid [3]. A stock solution was diluted to concentrations giving absorbance values ranging from 0.2 to 2.0. Based on the absorbance spectrum of potassium dichromate in 0.01 N sulfuric acid, absorbance was measured at 258 nm.

A correlation coefficient was calculated using the absorbanc values from the two weakest standard solutions; the same process was rep ated for

Rainbow Dynamic Dissolution Monitor™ ...*continued*

increasing strengths of standard solutions to determine the upper end of absorbance linearity (taken as 99.9% correlation with prediction).

Anticoagulant tablets

The Rainbow Dynamic Dissolution Monitor™ was evaluated using anticoagulant tablets containing 3 mg of active compound, corn starch white, lactose powder, magnesium stearate, and talc.

In routine dissolution analysis, the anticoagulant tablets are dissolved in 900 mL of artificial intestinal fluid pH 7.5 (comprised of 80.5g anhydrous dipotassium hydrogen phosphate and 15.6 g of potassium dihydrogen phosphate dihydrate in 10 liters of distilled water), stirred at 50 rpm in apparatus 2 [4]. The medium is degassed and heated to 37.0 ± 0.5 °C. The 20-minute Q value used for release analysis is 75% [5].

Linearity of absorbance readings

To identify a suitable detection wavelength, triplicate absorbance spectra were acquired of solutions equivalent to 25, 50, 75, 100, and 125% of active compound dissolved in artificial intestinal fluid pH 7.5, with approximate concentrations of 0.00083, 0.00167, 0.00250, 0.00333, and 0.00417 mg/mL, respectively. The resulting correlation coefficient was plotted against wavelength.

Linearity of compensation methods

Based on the absorbance and second derivative spectrum of active compound in artificial intestinal fluid pH 7.5 determined in an earlier experiment, the linearity of three different turbidity compensation methods was investigated (Table 1).

Table 1: Three different turbidity compensation methods.

Method	Type of spectrum used	Wavelengths [nm]
1	Absorbance	310 (detection) 350 (compensation)
2	Absorbance	310 (detection) 376 (compensation)
3	Second derivative	300 to 320

All methods were evaluated in triplicate using 25, 50, 75, 100, and 125% solutions of active compound dissolved in artificial intestinal fluid pH 7.5 with approximat concentrations of 0.00083, 0.00167, 0.00250, 0.00333, and 0.00417 mg/mL, respectively, and using clear medium as well as medium containing a concentration of placebo powder equivalent to one 130.0 mg tablet dissolved in 900 mL artificial intestinal fluid pH 7.5.

The validation of analytical methods (VoAM) program, version 3.0 [6], was used, with the following acceptance criteria [7, 8]: correlation coefficient > 0.99; y intercept within the 95% confidence interval of 2% of the reference x value (100% solution of active compound); precision, expressed as the standard deviation of relative repeatability (treating each set of triplicate data as one group), < 2.00% assuming data and mean recovery between 98.00 and 102.00%.

Comparison of turbidity compensation methods

Six absorbance readings of active compound solution in artificial intestinal fluid pH 7.5 before and after addition of placebo powder were acquired in triplicate to compare the accuracy and efficacy of the three turbidity compensation methods, using 100% solutions of active compound (approximately 0.00333 mg/mL).

The VoAM 3.0 program [6] was used to determine statistical equivalence, with the following acceptance criterion: the 95% confidence interval of the mean of the test method had to lie entirely within 2.00% either side of the mean of the reference method.

Robustness of the turbidity compensation methods

Two absorbance measurements were acquired at 12 different positions (hence different bending radii) of the fiber optic immersion probes and cables to test the robustness of each compensation method with respect to obligatory movement by the fiber optic immersion probes during the performance of a dissolution run. This experiment was performed using artificial intestinal fluid pH 7.5 containing active compound at approximately 0.00417 mg/mL, equivalent to the extent of dissolution of 125%.

Method comparison

The two turbidity compensation wavelength methods were compared in dissolution runs using a dissolution bath (Distek Premiere 5100, Distek Inc., North Brunswick, USA) and three lots of anticoagulant tablets (six tablets per lot). Active compound release was quantified at 20 minutes using the two turbidity compensation methods and the corresponding reference m thods. With the refer nce methods, a 20 mL aliquot was manually remov d

from each vessel and membran -filtered (0.45 µm pore size, Gelman Acrodisc, product no. 4496, Pall Gelman Sciences, Ann Arbor, USA) [5]. Single point calibration was used for quantification on a diode array spectrometer (HP 8452 A, Agilent Technologies, Rockaway, USA) in combination with the same compensation wavelength used with the Rainbow Dynamic Dissolution Monitor™.

Equivalence was defined as a maximum deviation of ± 2.0% per tablet, with post-calculation rounding.

Results

System suitability

Evidence for the suitability of fiber optic transmission and system linear range is given below.

Transmission

The plot of relative probe energy in artificial intestinal fluid pH 7.5 (Figure 1) shows values exceeding 30% from about 230 to 390 nm. Hence this wavelength range is suitable for measuring UV absorbance.

Linear range

The spectrum of potassium dichromate in 0.01 N sulfuric acid shows an absorbance maximum at 258 nm being used to evaluate linear range. Table 2 gives the upper limits of the linear ranges examined with potassium dichromate in 0.01 N sulfuric acid at 258 nm with all six probes (channels).

Since probes 4 to 6 showed values of 1.5 AU, the linear range of the whole system also had to be set to 1.5 AU.

Anticoagulant tablets

Linearity of the absorbance readings

Figure 2 plots the correlation coefficient against wavelength with active compound dissolved in artificial intestinal fluid pH 7.5 (25–125% solutions, with approximate concentrations of 0.00083–0.00417 mg/mL). The active compound absorbance spectrum in this figure indicates decreases in absorbance at 260 and 340 nm, arising from a decrease in system linearity owing to a decrease in system signal to noise ratio. The further slight decrease near 220 nm arises from the reduced energy available in the shortwave UV region.

It is clear that the whole wavelength range from 220 to 340 nm is suitable for method development

Linearity of turbidity compensation methods

Figure 3 (page 12) shows the UV absorbance spectrum of active compound and its stimate of the second derivative used in the Rainbow Dynamic Dissolution Monitor™ software.

Based on the absorbance spectrum with a maximum at 310 nm, two turbidity compensation methods using the peak wavelength and compensation wavelengths of 350 and 376 nm respectively were chosen. The 300–320 nm range was used in the case of the second derivative.

Table 3 (page 12) gives the relevant statistical

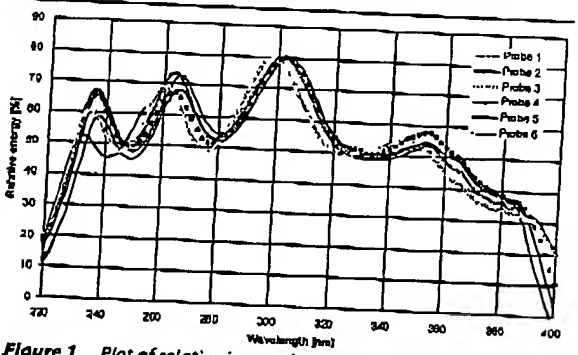

Figure 1 Plot of relative immersion probe energy in artificial intestinal fluid pH 7.5 against wavelength (nm)

Table 2: Upper end of linear range for all probes (channels).

Probe	Upper limit of linear range [absorbance units (AU)]
1	1.6
2	1.8
3	1.6
4	1.5
5	1.5
6	1.5

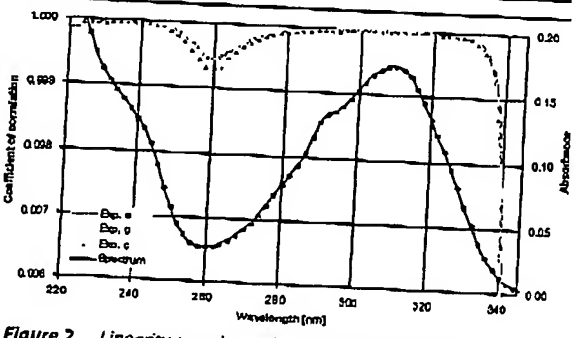

Figure 2 Linearity experiment in triplicate (a–c) with active compound at a concentration equivalent to 100% dissolution in artificial intestinal fluid pH 7.5 (approximately 0.00333 mg/ml): plot of correlation coefficient against wavelength, incorporating the absorbance spectrum of active compound

Rainbow Dynamic Dissolution Monitor™ ...*continued*

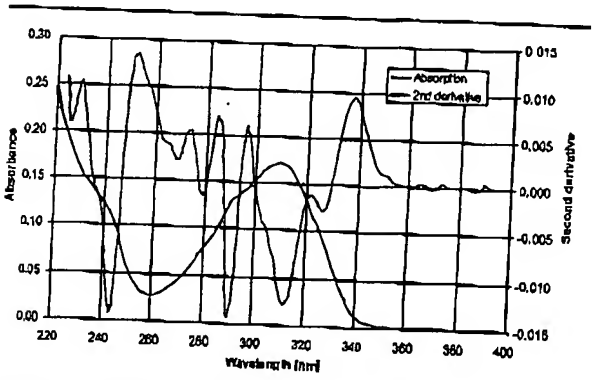

Figure 3 *Absorbance spectrum of active compound at a concentration equivalent to 100% dissolution in artificial intestinal fluid pH 7.5, co-plotted with its estimate for the second derivative used in the Rainbow Dynamic Dissolution Monitor™*

parameters for validating the three methods using clear as well as placebo-spiked solutions.

In the case of the clear solutions all parameters were inside the acceptance limits. There were no significant differences (p = 95%) in method validation. However, correlation coefficients were clearly lower, and standard deviations of relative repeatability and recovery rates clearly higher, with the second derivative method (Method 3) than with either compensation wavelength method (Methods 1 and 2). Therefore it can be concluded that the second derivative algorithm is less accurate and less precise than either wavelength method when examining clear solutions.

When performing the same method validation experiments with placebo-spiked solutions, there were air bubbles in the measurement compartments of probes 1 and 4 in at least one of the triplicate measurements. As can be seen in Figure 4, in contrast to the wavelength-indepen-

Table 3 *Statistical validation parameters for the three methods, based on one data set each for clear solutions and placebo-spiked medium*
Legend *r: correlation coefficient; SD_{rel}: standard deviation of relative repeatability; *: air bubbles in measurement window during the experiment; shading: value outside the acceptance limits.*

Method 1 (310 and 350 nm): clear solutions						
Parameter	Probe 1	Probe 2	Probe 3	Probe 4	Probe 5	Probe 6
r	0.99999	0.99999	0.99999	0.99994	0.99977	0.99997
SDrel [%]	0.15	0.13	0.15	0.14	0.16	0.12
Intercept	+	+	+	+	+	+
recovery [%]	100.16	100.01	100.13	100.26	101.03	100.04
Method 2 (310 and 376 nm): clear solutions						
Parameter	Probe 1	Probe 2	Probe 3	Probe 4	Probe 5	Probe 6
r	0.99999	0.99999	0.99999	0.99990	0.99968	0.99995
SDrel [%]	0.14	0.13	0.14	0.15	0.16	0.13
intercept	+	+	+	+	+	+
recovery [%]	100.12	100.02	99.88	100.19	101.29	100.04
Method 3 (derivative from 300 to 310 nm): clear solutions						
Parameter	Probe 1	Probe 2	Probe 3	Probe 4	Probe 5	Probe 6
r	0.99998	0.99992	0.99997	0.99996	0.99930	0.99997
SDrel [%]	0.22	0.23	0.25	0.26	0.26	0.22
Intercept	+	+	+	+	+	+
recovery [%]	101.45	101.26	101.39	101.62	101.18	101.16
Method 1 (310 and 350 nm): placebo-spiked, turbid solutions						
Parameter	Probe 1*	Probe 2	Probe 3	Probe 4*	Probe 5	Probe 6
r	0.99846	0.99879	0.99989	0.8973	0.99965	0.99983
SDrel [%]	0.58	0.35	0.21	0.28	0.16	0.23
intercept	+	+	+	+	+	+
recovery [%]	98.34	100.82	99.88	99.63	100.34	99.90
Method 2 (310 and 376 nm): placebo-spiked, turbid solutions						
Parameter	Probe 1*	Probe 2	Probe 3	Probe 4*	Probe 5	Probe 6
r	0.99673	0.99858	0.99985	0.98045	0.99938	0.99978
SDrel [%]	0.71	0.41	0.28	0.34	0.16	0.24
intercept	+	+	+	+	+	+
recovery [%]	96.93	100.67	99.51	99.17	99.99	99.47
Method 3 (derivative from 300 to 310 nm): placebo-spiked, turbid solutions						
Parameter	Probe 1*	Probe 2	Probe 3	Probe 4*	Probe 5	Probe 6
r	0.99972	0.99966	0.99970	0.99847	0.99927	0.99988
SDrel [%]	0.49	0.49	0.42	0.37	0.38	0.26
Intercept	+	+	+	+	+	+
recovery [%]	100.79	100.04	100.84	101.03	100.89	100.47

dent baseline offset caused by tablet excipients, air bubbles have a wavelength-dependent impact on the baseline owing to the wavelength dependency of refraction and diffraction. This explains why in Method 1, where the compensation wavelength approximates to the analytical wavelength, only probe 4 failed the validation acceptance limits; in Method 2, on the other hand, where the compensation wavelength is further from the analytical wavelength, probes 1 and 4 failed the acceptance criteria. Since the second derivative algorithm corrected for sloping baseline offsets, all probes met the acceptance criteria, making this the most robust method. Although there were no significant differences ($p = 95\%$) in method validation, the second derivative algorithm tended to have a slightly higher standard deviation of relative repeatability.

Based on the validation acceptance criteria for method equivalence there were no significant differences ($p = 95\%$) between the methods used for turbidity compensation. But as can be seen from Figure 5, which shows the mean concentrations of six measurements with their standard deviations as error bars for the three methods before and after addition of placebo powder, the two-wavelength compensation methods (methods 1 and 2) have a smaller standard deviation than the second derivative method (method 3) and show less probe to probe variation. Hence methods 1 and 2 are more rugged from this standpoint.

Since concentrations are higher before than after the addition of placebo powder, all three turbidity compensation methods overcompensate. Although the differences are not significant ($p = 95\%$) for method validation, the differences between clear and turbid solutions are smallest when using the two-wavelength method with a compensation wavelength approximating to the analytical wavelength. Hence method 1 is most suitable in terms of the accuracy of turbidity correction.

Robustness of turbidity compensation methods

Table 4 (page 16) shows that the method to method difference, expressed as the relative SD, was not significant ($p = 95\%$) in method validation. All three methods are therefore equivalent in terms of the robustness of moving fiber optic probes.

Method comparison

Every dosage form met the acceptance criteria using method 1 and 2 (Table 5, page 16). Both methods give accurate results on the Rainbow Dynamic Dissolution Monitor™.

Benefit analysis

Table 6 presents the results of a benefit analysis comparing the Rainbow Dynamic Dissolution Monitor™ with a conventional system using filtration and flow-through cuvettes to determine the amount of dissolved active compound, in terms of the following parameters: laboratory work, validation burden, maintenance, analytical information and GMP compliance. The total scores show that the Rainbow Dynamic Dissolution Monitor™ outperforms a semi-automatic filtering and flow-through cuvette measurement on-line system without loss of GMP compliance.

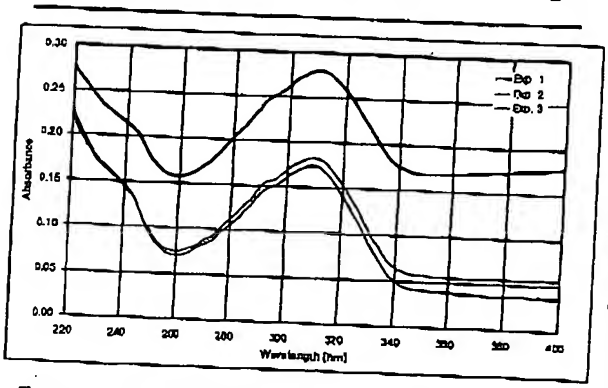

Figure 4 Probe 4: Absorbance spectra of measure 2 per triplicate (Methods 1–3) at a concentration equivalent to 75% dissolution (approximately 0.0025 mg/ml), comparing the wavelength-dependent baseline offset caused by air bubbles in the measuring compartment (Exp. 2 & 3) vs the air bubble-free spectrum (Exp. 1) which shows only the wavelength-independent offset caused by excipient turbidity.

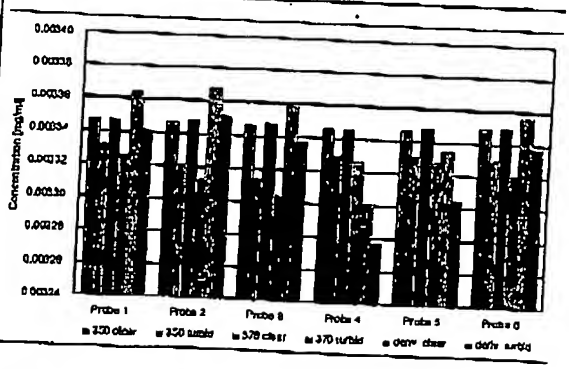

Figure 5 Concentrations measured using the three methods before and after addition of placebo powder (means of six measures). Error bars: 2 SD.

Rainbow Dynamic Dissolution Monitor™ ...*continued*

Laboratory work

Laboratory workload, in terms of preparing the bath and standards, is similar with both systems. During operation, no more hardware problems are to be expected with the Rainbow Dynamic Dissolution Monitor™ than with the conventional system since the fiber optic immersion probes and related mechanics are quite robust [9].

Table 4 Relative standard deviations (SD_{rel}) of two measurements in 12 positions per method

	Probe 1	Probe 2	Probe 3	Probe 4	Probe 5	Probe 6
	Method 1 (310 and 350 nm)					
SDrel [%]	0.16	0.14	0.11	0.08	0.09	0.08
	Method 2 (310 and 376 nm)					
SDrel [%]	0.20	0.19	0.14	0.10	0.11	0.10
	Method 3 (2nd derivative from 300 to 310 nm)					
SDrel [%]	0.14	0.16	0.16	0.12	0.11	0.16

Table 5 Amounts (%) of dissolved active compound using methods 1 and 2.
With the Hewlett-Packard spectrometer, sample absorbances were measured after filtration. Some calculated differences do not quite match the percentages in the results column due to the calculation being performed before rounding.

Lot 1	Method 1 (310 and 350 nm)			Method 2 (310 and 376 nm)		
Tablet	HP	Rainbow	Difference	HP	Rainbow	Difference
1	98.6	97.7	-0.9	98.4	98.4	-0.1
2	100.3	98.5	-1.8	100.4	99.0	-1.4
3	98.9	97.3	-1.6	98.9	97.9	-1.0
4	101.0	99.0	-1.9	100.6	99.0	-1.6
5	99.3	97.6	-1.8	99.0	97.6	-1.4
6	94.9	95.8	-0.9	95.5	94.9	-0.7
Lot 2	**Method 1 (310 and 350 nm)**			**Method 2 (310 and 376 nm)**		
Tablet	**HP**	**Rainbow**	**Difference**	**HP**	**Rainbow**	**Difference**
1	95.6	96.0	0.4	95.7	96.0	0.2
2	95.6	94.3	-1.3	95.6	94.3	-1.3
3	95.8	94.4	-1.4	95.9	94.4	-1.5
4	99.0	97.7	-1.3	99.0	97.7	-1.4
5	100.2	98.7	-1.5	99.8	98.7	-1.1
6	101.7	99.8	-1.9	101.4	99.8	-1.5
Lot 3	**Method 1 (310 and 350 nm)**			**Method 2 (310 and 376 nm)**		
Tablet	**HP**	**Rainbow**	**Difference**	**HP**	**Rainbow**	**Difference**
1	96.2	95.3	-0.8	96.4	96.1	-0.3
2	101.5	99.6	-1.9	101.9	100.0	-1.9
3	99.7	98.0	-1.7	99.7	98.3	-1.4
4	98.4	97.1	-1.3	98.6	97.5	-1.1
5	100.6	98.7	-1.9	100.9	98.9	-2.0
6	98.9	98.4	-0.5	100.1	98.9	-1.2

Qualification burden

Since the Rainbow Dynamic Dissolution Monitor™ incorporates no filtration facility or liquid pump, there is less equipment to qualify. The UV detectors are also simpler to qualify than spectrometers used for UV/VIS precision measurements [10].

Maintenance

The Rainbow Dynamic Dissolution Monitor™ is easier to maintain and less labor- intensive due to the elimination of sample removal and filtration.

Analytical information

The Rainbow Dynamic Dissolution Monitor™ can supply a data point every 10 seconds, giving dissolution profiles containing a lot of information. It also eliminates problems due to dead volume, time differences between sampling and measuring, and filter clogging, leading to greater accuracy.

GMP compliance

Both systems are GMP compliant.

Conclusions

The analytical results confirm that the Rainbow Dynamic Dissolution Monitor™ can be used to measure dissolution by methods which meet the acceptance criteria for linearity, accuracy, precision, and reproducibility stipulated in current validation of analytical methods guidelines [7]. Both instrument and software are GMP compliant. Benefit analysis shows that it outperforms dissolution measurement systems employing filtering and flow-through cells. The advantages have an impact on the high acquisition costs, though. The Rainbow Dynamic Dissolution Monitor™ is thus suitable for routine dissolution analysis in pharmaceutical quality control.

Both the two-wavelength compensation method and the second derivative algorithm are suitable for monitoring dissolution. The former is generally more precise and accurate, especially for non-disintegrating formulations where the medium stays clear. For formulations giving a background resulting in a sloping offset, the second derivative algorithm is preferable, as also when there are air bubble problems.

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Table 6 Benefit analysis: Rainbow Dynamic Dissolution Monitor™ vs a conventional on-line system, in terms of criteria ranked using a weighting factor (0–100%). Mark (1–5): system approximation to criteria. Score: weighting factor x mark.

Criterion	Weighting factor [%]	Rainbow		Conventional	
		Mark	Score	Mark	Score
Laboratory work	15	3	45	3	45
Qualification burden	15	4	60	2	30
Maintenance	15	3	45	2	30
Analytical information	15	5	75	2	30
GMP compliance	40	5	200	5	200
Total	100	20	425	14	335

	Hits	Search Text
1	3	"2001035947"
2	3	("2001035947").PN.
3	149	(multi$3 or multiple or plural$4) near3 "flow cell"
4	104	(multi$3 or multiple or plural$4) with (flow near2 cell$2) with (optic$3 or spectrophoto$5 or spectr$4)
5	1413	(multi$3 or multiple or plural$4) with (flow near2 cell$2)
6	690	(multi$3 or multiple or plural$4) near6 (flow near2 cell$2)
7	26947	(multi$3 or multiple or plural$4) near6 (optic$4 near2 fiber$2)
8	27	((multi$3 or multiple or plural$4) near6 (flow near2 cell$2)) and ((multi$3 or multiple or plural$4) near6 (optic$4 near2 fiber$2))
9	105	(flow near2 cell$2) and (fiber near2 optic$2) and dissolut$4
10	25	((flow near2 cell$2) and (fiber near2 optic$2) and dissolut$4) and remote
11	11	((flow near2 cell$2) and (fiber near2 optic$2) and dissolut$4) and ((multi$3 or multiple or plural$4) with (flow near2 cell$2))
12	419	(flow near2 cell$2) and (fiber near2 optic$2) and remot$4
13	27	((flow near2 cell$2) and (fiber near2 optic$2) and remot$4) and dissolut$5
14	1951	(fiber near3 optic$4) and (flow near3 cell$2)
15	24	((fiber near3 optic$4) and (flow near3 cell$2)) and (path near6 (perpendicular or transverse) near5 flow$4)

	Hits	Search Text
16	79	((plural$4 or multiple$3) near5 (flow near2 cell$2)) and (fiber near2 optic$4)
17	918	(flow near2 cell$2) and (fiber near2 optic$2) and reaction$4
18	837	((flow near2 cell$2) and (fiber near2 optic$2) and reaction$4) and (plural$4 or multipl$3)
19	176	(((flow near2 cell$2) and (fiber near2 optic$2) and reaction$4) and (plural$4 or multipl$3)) and remote
20	561	(multi$3 or multiple or plural$4) near4 (flow near2 cell$2)
21	67	((multi$3 or multiple or plural$4) near4 (flow near2 cell$2)) and (fiber near2 optic$4)
22	4	(("5498324") or ("5324401")).PN.
23	332	(flow near2 cell$2) and (fiber near2 optic$2) and (dissolution or concentrtaion or dissolving)
24	270	((flow near2 cell$2) and (fiber near2 optic$2) and (dissolution or concentrtaion or dissolving)) and (((flow near2 cell$2) and (fiber near2 optic$2) and reaction$4) and (plural$4 or multipl$3))
25	332	(flow near2 cell$2) and (fiber near2 optic$2) and (dissolution or dissolving)
26	113	((flow near2 cell$2) and (fiber near2 optic$2) and (dissolution or dissolving)) and mirror$2
27	4	((multi$3 or multiple or plural$4) near4 (flow near2 cell$2)) and (((flow near2 cell$2) and (fiber near2 optic$2) and (dissolution or dissolving)) and mirror$2)
28	2	("6174497").PN.
29	2	("6060024").PN.
30	2	("6174497").PN.

	Hits	Search Text
31	2134	(422/82.05-82.09).CCLS.
32	338	((422/82.05-82.09).CCLS.) and (flow near2 cell$2)

Mellerson, Kendra

From: Gakh, Yelena
Sent: Monday, November 17, 2003 8:16 PM
To: STIC-EIC1700
Subject: 10014270

Dear Kendra,

please submit the following:

TITLE: Evaluation of the rainbow dynamic dissolution monitor semi-automatic fiber optic dissolution tester
AUTHOR(S): Schatz, Caspar; Ulmschneider, Michel; Altermatt, Rolf; Marrer, Stephan
CORPORATE SOURCE: Pharmaceutical Quality Assurance and Quality Control, F. Hoffmann-La Roche Ltd., Basel, Switz.
SOURCE: Dissolution Technologies (2000), 7(4), 8, 10-12, 14, 16-17

Thanks,

yelena

Yelena G. Gakh, Ph.D.

Patent Examiner
USPTO, cp3/7B-08
(703)306-5906

Evaluation of the Rainbow Dynamic Dissolution Monitor™ Semi-automatic Fiber Optic Dissolution Tester

Caspar Schatz, Michel Ulmschneider, Rolf Altermatt, Stephan Marrer
Pharmaceutical Quality Assurance and Quality Control, F. Hoffmann-La Roche Ltd, Basel, Switzerland

email:caspar.schatz@roche.com

Summary
The Rainbow Dynamic Dissolution Monitor™ (Delphian Technology LP, Ardsley, USA) is a simple and convenient UV absorbance technique for acquiring precise, accurate, reproducible and robust dissolution profiles of drug formulations containing a single active ingredient. The instrument and its software are GMP compliant. Benefit analysis shows that it has significant advantages for dissolution over systems using filtering and flow -through cells. The Rainbow Dynamic Dissolution Monitor™ is thus suitable for routine dissolution analysis in pharmaceutical quality control.

Introduction
The Rainbow Dynamic Dissolution Monitor™ uses 12 fiber optic immersion probes residing in vessels of two dissolution baths throughout the dissolution test. Two deuterium lamps are used as a light source. After interacting with the sample, the light is guided to a series of 12 photo diode array ultraviolet monolithic miniature spectrometers (UV MMS, Carl Zeiss, Jena, Germany) [1] which measure from 200 to 400 nm with an absolute wavelength accuracy of 0.2 nm and a temperature drift less than 0.005 nm/K. The spectral pixel spacing is 0.8 nm, giving a Rayleigh resolution of about 3 nm. Stray light measured at 240 nm using a deuterium lamp and potassium iodide solution (10 g/l) is 0.3 % [2]. Each spectrometer unit and its probe are referred to as a channel.

Before performing a dissolution run the system collects 0% and 100 % transmission blanks and standard absorbance scans per channel. Hence the amount of dissolved active compound is determined with a single point calibration. To eliminate standard preparation errors, a second quality control standard is measured for control purposes only. During a run, the system can acquire absorbance scans every 10 seconds. The software incorporates two methods to correct for turbidity and scattering effects. The first method uses two wavelengths: one to determine the active compound, the other to act as a compensation wavelength. The second method is based on a second derivative algorithm using a wavelength range [1]. It uses a very simple algorithm to estimate the second derivative and a form of co-addition of several wavelengths to improve the signal to noise ratio.

Experimental
All the experiments were performed using the Rainbow Dynamic Dissolution Monitor™ with 10 mm pathlength Hellma ultra mini-immersion probes, (type 661.673-UV, Hellma GmbH & Co.,

Müllheim/Baden, Germany) to acquire UV measurements. Only six channels/probes were evaluated, always using one scan per measurement in each case.

System suitability

Suitability was assessed in terms of fiber optic unit transmission and the linear range of the spectroscopic assembly.

Transmission

The relative energy of 100% transmission spectra of artificial intestinal fluid pH 7.5 (reference Anticoagulant Tablets Section, page 10, for fluid composition) was plotted against wavelength as a measure of channel and probe transmission

Linear range

The linear range of all six evaluated channels was tested using a dilution series of potassium dichromate (spectroscopy grade, Fluka Chemie AG, Buchs, Switzerland) in 0.01 N sulphuric acid [3]. A stock solution was diluted to concentrations giving absorbance values ranging from 0.2 to 2.0. Based on the absorbance spectrum of potassium dichromate in 0.01 N sulphuric acid, absorbance was measured at 258 nm.
A correlation coefficient was calculated using the absorbance values from the two weakest standard solutions; the same process was repeated for increasing strengths of standard solutions to determine the upper end of absorbance linearity (taken as 99.9% correlation with prediction).

Anticoagulant tablets

The Rainbow Dynamic Dissolution Monitor™ was evaluated using anticoagulant tablets containing 3 mg of active compound, corn starch white, lactose powder, magnesium stearate, and talc.

In routine dissolution analysis, the anticoagulant tablets are dissolved in 900 ml of artificial intestinal fluid pH 7.5 (comprised of 80.5g anhydrous dipotassium hydrogen phosphate and 15.6 g of potassium dihydrogen phosphate dihydrate in 10 liters ofdistilled water), stirred at 50 rpm in apparatus 2 [4]. The medium is degassed and heated to 37.0 ± 0.5 °C. The 20-minute Q value used for release analysis is 75% [5].

Linearity of absorbance readings

To identify a suitable detection wavelength, triplicate absorbance spectra were acquired of solutions equivalent to 25, 50, 75, 100, and 125% of active compound dissolved in artificial intestinal fluid pH 7.5, with approximate concentrations of 0.00083, 0.00167, 0.00250, 0.00333, and 0.00417 mg/ml, respectively. The resulting correlation coefficient was plotted against wavelength.

Linearity of compensation methods

Based on the absorbance and second derivative spectrum of active compound in artificial intestinal fluid pH 7.5 determined in an earlier experiment, the linearity of three different turbidity compensation methods was investigated *(Table 1)*.

Table 1: Three different turbidity compensation methods.

Method	Type of spectrum used	Wavelengths [nm]

1	Absorbance	310 (detection) 350 (compensation)
2	Absorbance	310 (detection) 376 (compensation)
3	Second derivative	300 to 320

All methods were evaluated in triplicate using 25, 50, 75, 100, and 125% solutions of active compound dissolved in artificial intestinal fluid pH 7.5 with approximate concentrations of 0.00083, 0.00167, 0.00250, 0.00333, and 0.00417 mg/ml, respectively, and using clear medium as well as medium containing a concentration of placebo powder equivalent to one 130.0 mg tablet dissolved in 900 ml artificial intestinal fluid pH 7.5.

The validation of analytical methods (VoAM) program, version 3.0 [6], was used, with the following acceptance criteria [7, 8]: correlation coefficient > 0.99; y intercept within the 95% confidence interval of 2% of the reference x value (100% solution of active compound); precision, expressed as the standard deviation of relative repeatability (treating each set of triplicate data as one group), < 2.00% assuming data and mean recovery between 98.00 and 102.00%.

Comparison of turbidity compensation methods

Six absorbance readings of active compound solution in artificial intestinal fluid pH 7.5 before and after addition of placebo powder were acquired in triplicate to compare the accuracy and efficacy of the three turbidity compensation methods, using 100% solutions of active compound (approximately 0.00333 mg/ml).

The VoAM 3.0 program [6] was used to determine statistical equivalence, with the following acceptance criterion: the 95% confidence interval of the mean of the test method had to lie entirely within 2.00% either side of the mean of the reference method.

Robustness of the turbidity compensation methods

Two absorbance measurements were acquired at 12 different positions (hence different bending radii) of the fiber optic immersion probes and cables to test the robustness of each compensation method with respect to obligatory movement by the fiber optic immersion probes during the performance of a dissolution run. This experiment was performed using artificial intestinal fluid pH 7.5 containing active compound at approximately 0.00417 mg/ml, equivalent to the extent of dissolution of 125%.

Method comparison

The two turbidity compensation wavelength methods were compared in dissolution runs using a dissolution bath (Distek Premiere 5100, Distek Inc., North Brunswick, USA) and three lots of anticoagulant tablets (six tablets per lot). Active compound release was quantified at 20 minutes using the two turbidity compensation methods and the corresponding reference methods. With the reference methods, a 20 ml aliquot was manually removed from each vessel and membrane-filtered (0.45 mm pore size, Gelman Acrodisc, product no. 4496, Pall Gelman Sciences, Ann Arbor, USA) [5]. Single point calibration was used for quantification on a diode array spectrometer (HP 8452 A, Agilent Technologies, Rockaway, USA) in combination with the same compensation wavelength used with the Rainbow Dynamic Dissolution Monitor™.

Equivalence was defined as a maximum deviation of ± 2.0% per tablet, with post-calculation rounding.

Results

System suitability

Evidence for the suitability of fiber optic transmission and system linear range is given below.

Transmission

The plot of relative probe energy in artificial intestinal fluid pH 7.5 *(Figure 1)* shows values exceeding 30% from about 230 to 390 nm. Hence this wavelength range is suitable for measuring UV absorbance.

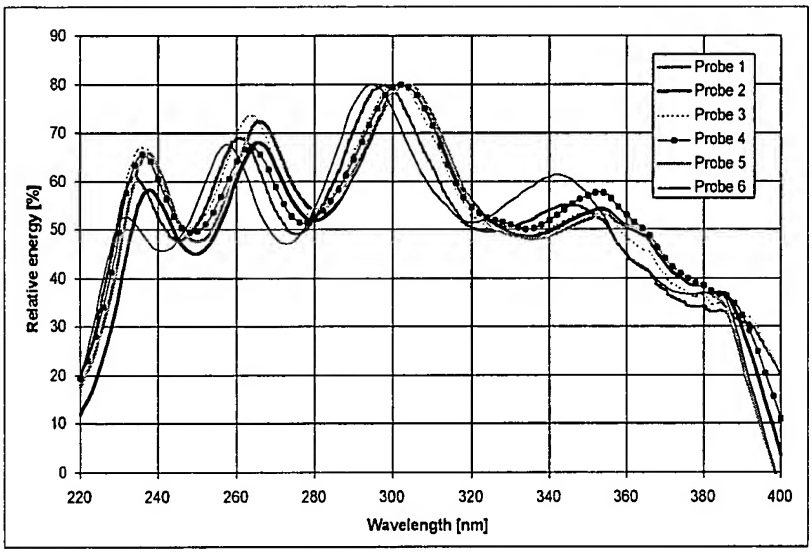

Figure 1 Plot of relative immersion probe energy in artificial intestinal fluid pH 7.5 against wavelength (nm)

Linear range

The spectrum of potassium dichromate in 0.01 N sulphuric acid shows an absorbance maximum at 258 nm being used to evaluate linear range. *Table 2* gives the upper limits of the linear ranges examined with potassium dichromate in 0.01 N sulphuric acid at 258 nm with all six probes (channels).

Table 2: Upper end of linear range for all probes (channels).

Probe	Upper limit of linear range [absorbance units (AU)]
1	1.6
2	1.8
3	1.6
4	1.5
5	1.5

6	1.5

Since probes 4 to 6 showed values of 1.5 AU, the linear range of the whole system also had to be set to 1.5 AU.

Anticoagulant tablets

Linearity of the absorbance readings

Figure 2 plots the correlation coefficient against wavelength with active compound dissolved in artificial intestinal fluid pH 7.5 (25125% solutions, with approximate concentrations of 0.00083 0.00417 mg/ml). The active compound absorbance spectrum in this figure indicates decreases in absorbance at 260 and 340 nm, arising from a decrease in system linearity owing to a decrease in system signal to noise ratio. The further slight decrease near 220 nm arises from the reduced energy available in the shortwave UV region.

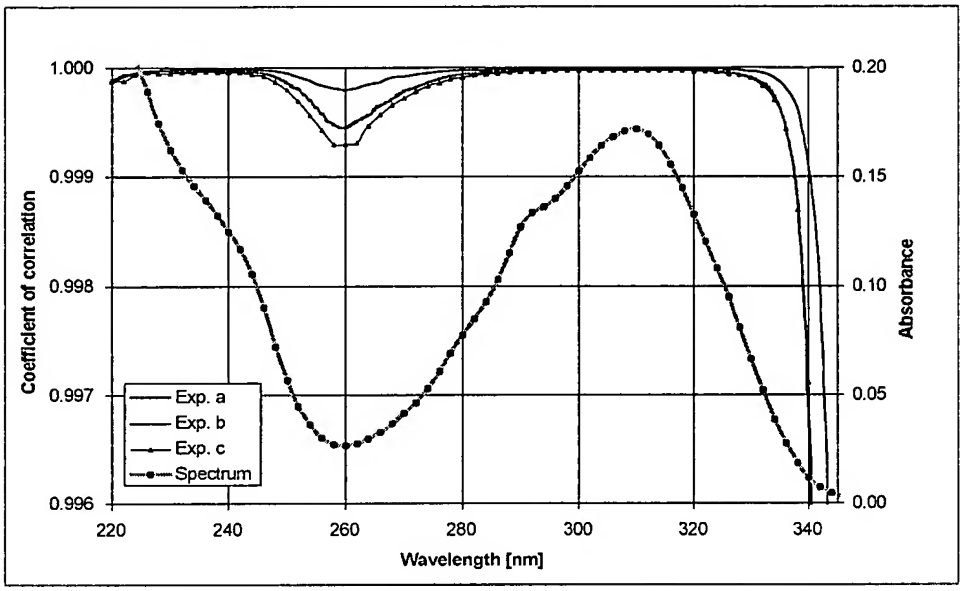

Figure 2 Linearity experiment in triplicate (ac) with active compound at a concentration equivalent to 100% dissolution in artificial intestinal fluid pH 7.5 (approximately 0.00333 mg/ml): plot of correlation coefficient against wavelength, incorporating the absorbance spectrum of active compound

It is clear that the whole wavelength range from 220 to 340 nm is suitable for method development

Linearity of turbidity compensation methods

Figure 3 shows the UV absorbance spectrum of active compound and its estimate of the second derivative used in the Rainbow Dynamic Dissolution Monitor™ software.
Based on the absorbance spectrum with a maximum at 310 nm, two turbidity compensation methods using the peak wavelength and compensation wavelengths of 350 and 376 nm respectively were chosen. The 300320 nm range was used in the case of the second derivative.

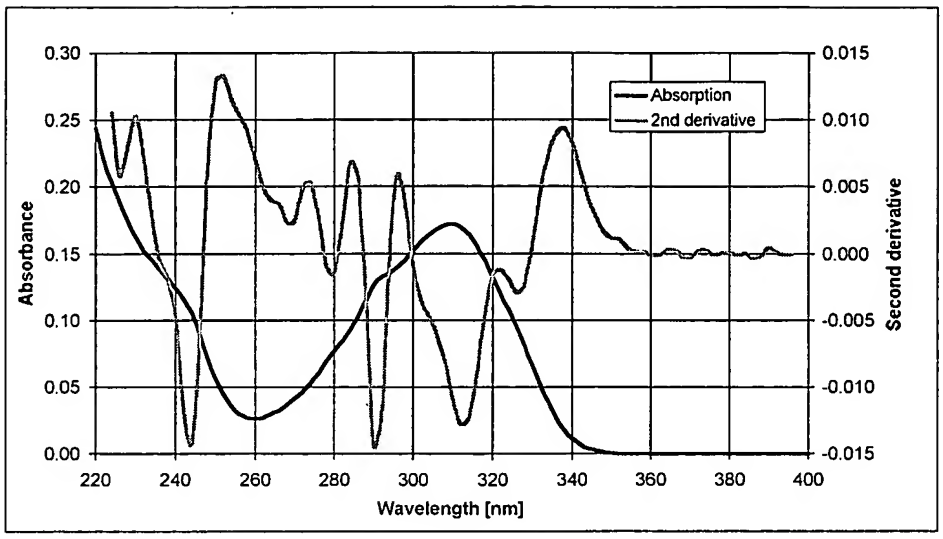

Figure 3 Absorbance spectrum of active compound at a concentration equivalent to 100% dissolution in artificial intestinal fluid pH 7.5, co-plotted with its estimate for the second derivative used in the Rainbow Dynamic Dissolution Monitor'

Table 3 gives the relevant statistical parameters for validating the three methods using clear as well as placebo-spiked solutions.

Method 1 (310 and 350 nm): clear solutions						
Parameter	**Probe 1**	**Probe 2**	**Probe 3**	**Probe 4**	**Probe 5**	**Probe 6**
r	0.99999	0.99999	0.99999	0.99994	0.99977	0.99997
SDrel [%]	0.15	0.13	0.15	0.14	0.16	0.12
intercept	+	+	+	+	+	+
recovery [%]	100.16	100.01	100.13	100.26	101.03	100.04
Method 2 (310 and 376 nm): clear solutions						
Parameter	**Probe 1**	**Probe 2**	**Probe 3**	**Probe 4**	**Probe 5**	**Probe 6**
r	0.99999	0.99999	0.99999	0.99990	0.99968	0.99995
SDrel [%]	0.14	0.13	0.14	0.15	0.16	0.13
intercept	+	+	+	+	+	+
recovery [%]	100.12	100.02	99.88	100.19	101.29	100.04
Method 3 (derivative from 300 to 310 nm): clear solutions						
Parameter	**Probe 1**	**Probe 2**	**Probe 3**	**Probe 4**	**Probe 5**	**Probe 6**
r	0.99998	0.99992	0.99997	0.99996	0.99930	0.99997
SDrel [%]	0.22	0.23	0.25	0.26	0.26	0.22

intercept	+	+	+	+	+	+
recovery [%]	101.45	101.26	101.39	101.62	101.18	101.16
Method 1 (310 and 350 nm): placebo-spiked, turbid solutions						
Parameter	**Probe 1***	**Probe 2**	**Probe 3**	**Probe 4***	**Probe 5**	**Probe 6**
r	0.99846	0.99879	0.99989	0.8973	0.99965	0.99983
SDrel [%]	0.58	0.35	0.21	0.28	0.16	0.23
intercept	+	+	+	-	+	+
recovery [%]	98.34	100.82	99.88	99.63	100.34	99.90
Method 2 (310 and 376 nm): placebo-spiked, turbid solutions						
Parameter	**Probe 1***	**Probe 2**	**Probe 3**	**Probe 4***	**Probe 5**	**Probe 6**
r	0.99673	0.99858	0.99985	0.98045	0.99938	0.99978
SDrel [%]	0.71	0.41	0.28	0.34	0.16	0.24
intercept	-	+	+	-	+	+
recovery [%]	96.93	100.67	99.51	99.17	99.99	99.47
Method 3 (derivative from 300 to 310 nm): placebo-spiked, turbid solutions						
Parameter	**Probe 1***	**Probe 2**	**Probe 3**	**Probe 4***	**Probe 5**	**Probe 6**
r	0.99972	0.99966	0.99970	0.99847	0.99927	0.99988
SDrel [%]	0.49	0.49	0.42	0.37	0.38	0.26
intercept	+	+	+	+	+	+
recovery [%]	100.79	100.04	100.84	101.03	100.89	100.47

In the case of the clear solutions all parameters were inside the acceptance limits. There were no significant differences (p = 95%) in method validation. However, correlation coefficients were clearly lower, and standard deviations of relative repeatability and recovery rates clearly higher, with the second derivative method (Method 3) than with either compensation wavelength method (Methods 1 and 2). Therefore it can be concluded that the second derivative algorithm is less accurate and less precise than either wavelength method when examining clear solutions.

When performing the same method validation experiments with placebo-spiked solutions, there were air bubbles in the measurement compartments of probes 1 and 4 in at least one of the triplicate measurements. As can be seen in *Figure 4,* in contrast to the wavelength-independent baseline offset caused by tablet excipients, air bubbles have a wavelength-dependent impact on the baseline owing to

the wavelength dependency of refraction and diffraction. This explains why in Method 1, where the compensation wavelength approximates to the analytical wavelength, only probe 4 failed the validation acceptance limits; in Method 2, on the other hand, where the compensation wavelength is further from the analytical wavelength, probes 1 and 4 failed the acceptance criteria. Since the second derivative algorithm corrected for sloping baseline offsets, all probes met the acceptance criteria, making this the most robust method. Although there were no significant differences (p = 95%) in method validation, the second derivative algorithm tended to have a slightly higher standard deviation of relative repeatability.

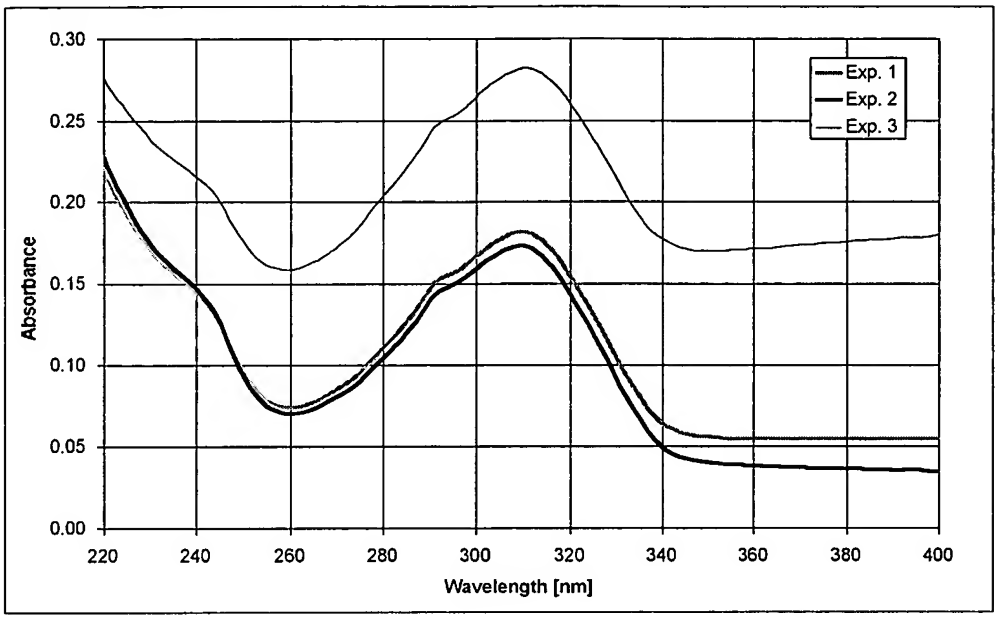

Figure 4 Probe 4: Absorbance spectra of measure 2 per triplicate (Methods 13) at a concentration equivalent to 75% dissolution (approximately 0.0025 mg/ml), comparing the wavelength-dependent baseline offset caused by air bubbles in the measuring compartment (Expts. 2 & 3) vs the air bubble-free spectrum (Expt. 1) which shows only the wavelength-independent offset caused by excipient turbidity.

Based on the validation acceptance criteria for method equivalence there were no significant differences (p = 95%) between the methods used for turbidity compensation. But as can be seen from *Figure 5*, which shows the mean concentrations of six measurements with their standard deviations as error bars for the three methods before and after addition of placebo powder, the two-wavelength compensation methods (methods 1 and 2) have a smaller standard deviation than the second derivative method (method 3) and show less probe to probe variation. Hence methods 1 and 2 are more rugged from this standpoint.

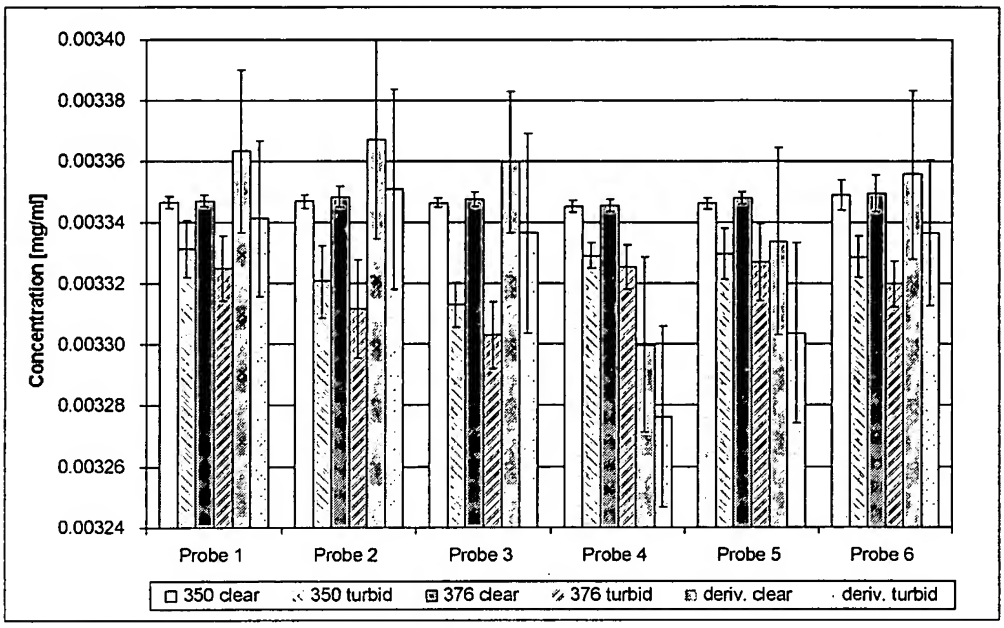

Figure 5 Concentrations measured using the three methods before and after addition of placebo powder (means of six measures). Error bars: 2 SD.

Since concentrations are higher before than after the addition of placebo powder, all three turbidity compensation methods overcompensate. Although the differences are not significant (p = 95%) for method validation, the differences between clear and turbid solutions are smallest when using the two-wavelength method with a compensation wavelength approximating to the analytical wavelength. Hence method 1 is most suitable in terms of the accuracy of turbidity correction.
Robustness of turbidity compensation methods

Table 4 shows that the method to method difference, expressed as the relative SD, was not significant (p = 95%) in method validation. All three methods are therefore equivalent in terms of the robustness of moving fiber optic probes.

Table 4 Relative standard deviations (SDrel) of two measurements in 12 positions per method

Method 1 (310 and 350 nm)						
	Probe 1	**Probe 2**	**Probe 3**	**Probe 4**	**Probe 5**	**Probe 6**
SDrel [%]	0.16	0.14	0.11	0.08	0.09	0.08
Method 2 (310 and 376 nm)						
	Probe 1	**Probe 2**	**Probe 3**	**Probe 4**	**Probe 5**	**Probe 6**
SDrel [%]	0.20	0.19	0.14	0.10	0.11	0.10
Method 3 (2nd derivative from 300 to 310 nm)						
	Probe 1	**Probe 2**	**Probe 3**	**Probe 4**	**Probe 5**	**Probe 6**
SDrel [%]	0.14	0.16	0.16	0.12	0.11	0.16

Method comparison

Every dosage form met the acceptance criteria using method 1 and 2 (*Table 5*). Both methods give accurate results on the Rainbow Dynamic Dissolution Monitor™.

Table 5 Amounts (%) of dissolved active compound using methods 1 and 2. With the Hewlett-Packard spectrometer, sample absorbances were measured after filtration. Some calculated differences do not quite match the percentages in the results column due to the calculation being performed before rounding.

Lot 1	Method 1 (310 and 350 nm)			Method 2 (310 and 376 nm)		
Tablet	**HP**	**Rainbow**	**Difference**	**HP**	**Rainbow**	**Difference**
1	98.6	97.7	-0.9	98.4	98.4	-0.1
2	100.3	98.5	-1.8	100.4	99.0	-1.4
3	98.9	97.3	-1.6	98.9	97.9	-1.0
4	101.0	99.0	-1.9	100.6	99.0	-1.6
5	99.3	97.6	-1.8	99.0	97.6	-1.4
6	94.9	95.8	-0.9	95.5	94.9	-0.7
Lot 2	**Method 1 (310 and 350 nm)**			**Method 2 (310 and 376 nm)**		
Tablet	**HP**	**Rainbow**	**Difference**	**HP**	**Rainbow**	**Difference**
1	95.6	96.0	0.4	95.7	96.0	0.2
2	95.6	94.3	-1.3	95.6	94.3	-1.3
3	95.8	94.4	-1.4	95.9	94.4	-1.5
4	99.0	97.7	-1.3	99.0	97.7	-1.4
5	100.2	98.7	-1.5	99.8	98.7	-1.1
6	101.7	99.8	-1.9	101.4	99.8	-1.5
Lot 3	**Method 1 (310 and 350 nm)**			**Method 2 (310 and 376 nm)**		
Tablet	**HP**	**Rainbow**	**Difference**	**HP**	**Rainbow**	**Difference**
1	96.2	95.3	-0.8	96.4	96.1	-0.3
2	101.5	99.6	-1.9	101.9	100.0	-1.9
3	99.7	98.0	-1.7	99.7	98.3	-1.4
4	98.4	97.1	-1.3	98.6	97.5	-1.1
5	100.6	98.7	-1.9	100.9	98.9	-2.0
6	98.9	98.4	-0.5	100.1	98.9	-1.2

Benefit analysis

Table 6 presents the results of a benefit analysis comparing the Rainbow Dynamic Dissolution Monitor™ with a conventional system using filtration and flow-through cuvettes to determine the amount of dissolved active compound, in terms of the following parameters: laboratory work,

validation burden, maintenance, analytical information and GMP compliance.The total scores show that the Rainbow Dynamic Dissolution Monitor™ outperforms a semi-automatic filtering and flow-through cuvette measurement on-line system without loss of GMP compliance.

Table 6 Benefit analysis: Rainbow Dynamic Dissolution MonitorÔ *vs* a conventional online system, in terms of criteria ranked using a weighting factor (0-100%). Mark (1-5): system approximation to criteria. Score: weighting factor x mark.

Criterion	Weighting factor [%]	Rainbow		Conventional	
		Mark	Score	Mark	Score
Laboratory work	15	3	45	3	45
Qualification burden	15	4	60	2	30
Maintenance	15	3	45	2	30
Analytical information	15	5	75	2	30
GMP compliance	40	5	200	5	200
Total	100	20	425	14	335

Laboratory work

Laboratory workload, in terms of preparing the bath and standards, is similar with both systems. During operation, no more hardware problems are to be expected with the Rainbow Dynamic Dissolution Monitor™ than with the conventional system since the fiber optic immersion probes and related mechanics are quite robust [9].

Qualification burden

Since the Rainbow Dynamic Dissolution Monitor™ incorporates no filtration facility or liquid pump, there is less equipment to qualify. The UV detectors are also simpler to qualify than spectrometers used for UV/VIS precision measurements [10].

Maintenance

The Rainbow Dynamic Dissolution Monitor™ is easier to maintain and less labor- intensive due to the elimination of sample removal and filtration.

Analytical information

The Rainbow Dynamic Dissolution Monitor™ can supply a data point every 10 seconds, giving dissolution profiles containing a lot of information. It also eliminates problems due to dead volume, time differences between sampling and measuring, and filter clogging, leading to greater accuracy.

GMP compliance

Both systems are GMP compliant.

Conclusions

The analytical results confirm that the Rainbow Dynamic Dissolution Monitor™ can be used to measure dissolution by methods which meet the acceptance criteria for linearity, accuracy, precision, and reproducibility stipulated in current validation of analytical methods guidelines [7]. Both instrument and software are GMP compliant. Benefit analysis shows that it outperforms dissolution measurement systems employing filtering and flow-through cells. The advantages have an impact on the high acquisition costs, though. The Rainbow Dynamic Dissolution Monitor™ is thus suitable for routine dissolution analysis in pharmaceutical quality control.

Both the two-wavelength compensation method and the second derivative algorithm are suitable for monitoring dissolution. The former is generally more precise and accurate, especially for non-disintegrating formulations where the medium stays clear. For formulations giving a background resulting in a sloping offset, the second derivative algorithm is preferable, as also when there are air bubble problems.

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http://www.varianinc.com/image/vimage/docs/products/spectr/uv/brochure/1520bro.pdf

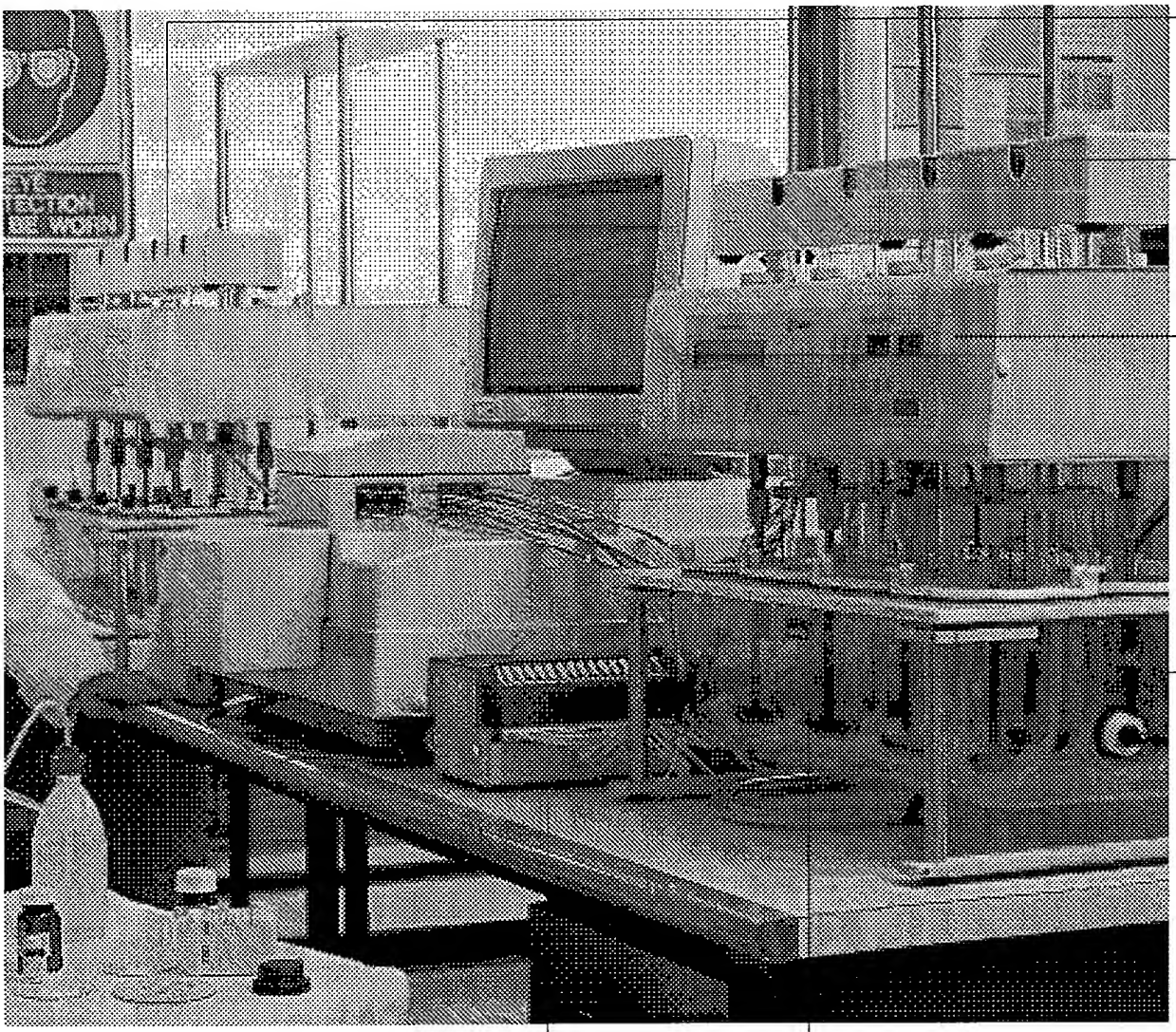
CARY AND VANKEL - A COMBINATION OF EXPERTS

Cary and VanKel have combined forces to provide one of the most innovative and flexible Tablet Dissolution systems on the market. With over 50 years experience in UV-Vis spectrometry, Varian is a leader in the field. VanKel is in a similar situation in the Dissolution tester market, so it makes sense to combine a Cary spectrophotometer with the VanKel Dissolution tester to form a complete Tablet Dissolution system.

To make up the system, Varian provides a Cary UV-Vis spectrophotometer, all the required spectrophotometer accessories, cuvettes and Tablet Dissolution software. VanKel supplies the Dissolution tester(s), water bath heater/circulator and the multichannel pump. The system can be set up with one or two Dissolution testers connected.

Major software features

- Easy to use Microsoft 32-bit Windows 95® compatible software
- You can connect up to 2 baths simultaneously
- You have the ability to swap between 2 different pathlength cells
- Up to 3 time regions can be specified for varying data collection rates
- Dissolution runs can be monitored for up to 12000 minutes (> 8 days)
- Single standard and multi standard calibrations are supported
- The user has up to 20 control limits to identify whether samples are out of pharmacopoeia specification, both graphically and in generated reports
- The variability of the standard measurements can be monitored during the run. The system will warn the operator if limits are exceeded
- Infinity measurements are supported by rotating the paddles/baskets at maximum speed for a user-specified time prior to taking the final readings
- A diagnostics tool for checking the communication status of the hardware is included
- You can perform weight correction calculations
- Up to 100 Time points for reporting can be set up
- Up to 100 %Dissolved points for reporting can be set up



Supports fully automated operation of up to 2 VK-7000 dissolution testers

The tablets can be automatically dropped

The bath can be programmed to warm up at a specified time. The bath temperature is fully controlled by the Cary software.

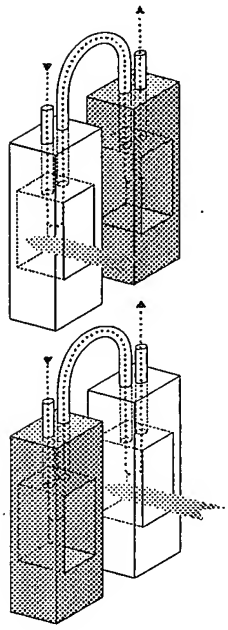
Both Basket and Paddle methods are supported.

The 1 tester system supports up to 8 vessels for online measurement of Blank and Standard solutions. Each tester in a two-tester system supports 6 samples and either a Blank or a Standard.

- **Both online and offline reporting are supported**
- **Audit trails are logged with all data, providing information about how the data was collected and/or calculated**
- **Method parameters can be specified in either hours or minutes to cater for slow or fast dissolving samples**
- **Data can be converted into ASCII format with or without an audit log**
- **The Report generator uses all the standard Windows 95® text editing capabilities**
- **You can choose to display %Dissolved vs Time, Absorbance vs Time and mg Dissolved vs Time graphics**

Automatic reversing of the pump at the end of each set of readings clears filters of any solids, preventing blockages. The pump stops for a user-defined period of time before readings are taken to allow bubbles to disperse.

Fast rotation of paddles/baskets before collecting data disperses bubbles. Stir speed is controlled by the software



Setting up a system with two different pathlengths relies upon the ability to reverse the beam mode of the Cary.

Cells of one pathlength are placed in the front cell positions and cells of another pathlength are placed in the rear cell positions. The cells that are not being measured just become extra tubing length.

What is included in the Cary Software?
The Cary Tablet package is available for the Cary 100 and 300 instruments. It packages the instrument with several software applications, including:

Dissolution application: to perform your tablet dissolution measurements.

Concentration application: to create multi standard calibrations for your dissolution runs.

Validation application: to validate the performance of your spectrophotometer.

GLP application: to set up different privileges for the users in your laboratory and comply with Good Laboratory Practice.

Scanning application: to perform routine wavelength scanning measurements.

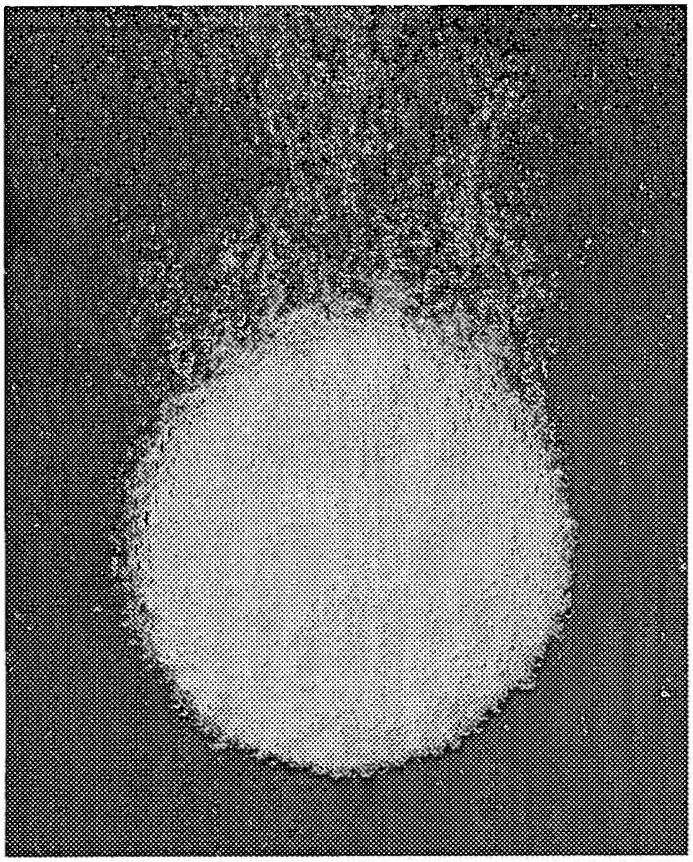
Simple Reads application: to measure the photometric value of samples at fixed wavelengths.

System Information application: to specify your company logo and information, as well as your hardware information (e.g. serial number, instrument model), for reporting purposes.

Which dissolution method is used?
The Cary Dissolution system uses the 'Flow-through' method to measure samples in real time. Unlike HPLC methods, this offers excellent productivity and produces no organic waste.

The flow-through method has two major advantages over the multi-port UV-Vis dissolution method:

• The multi-port method reduces the volume of each vessel with each measurement, creating the possibility of precipitation of the active ingredient, resulting in the inability to complete the analysis. The flow-through method keeps the volume of the vessels constant throughout the entire run by recycling the solution back into the vessels.

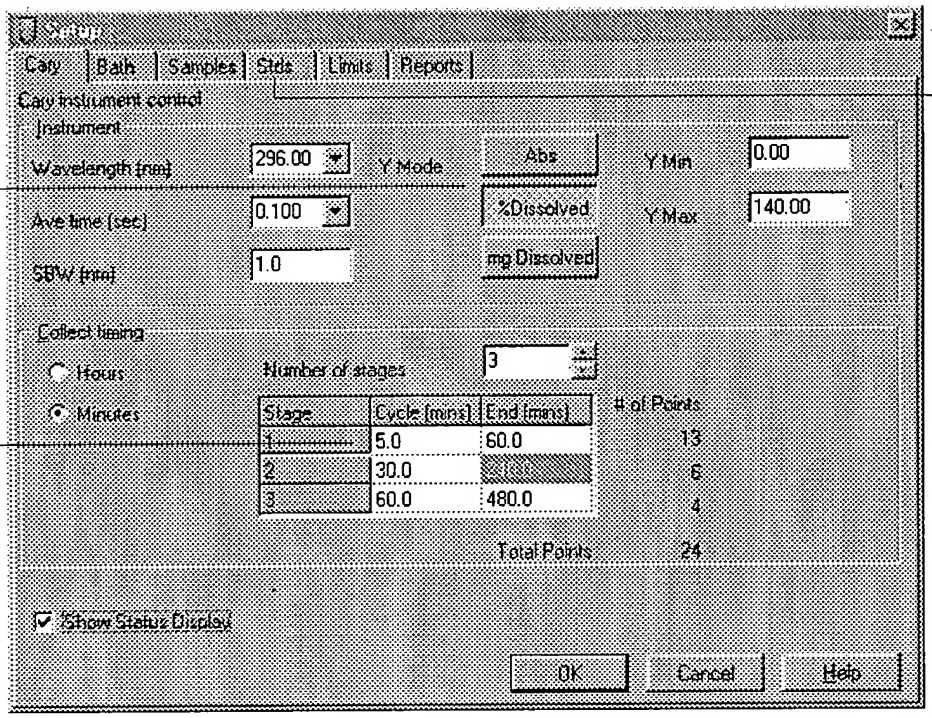


• The multi-port method uses one flow cell for all 6 samples, hence there is a high risk of cross contamination between samples.

Also, since the multi-port method measures samples in sequence, this method cannot be used to analyse very fast dissolving samples. In comparison, the flow-through method allows each sample to be measured once every minute.

The multi-port method does offer high sample throughput, by providing the ability to measure multiple testers during one run, however, with the release of the Cary VanKel two tester system you can have the best of both worlds – all the advantages of the flow-through method plus high productivity!

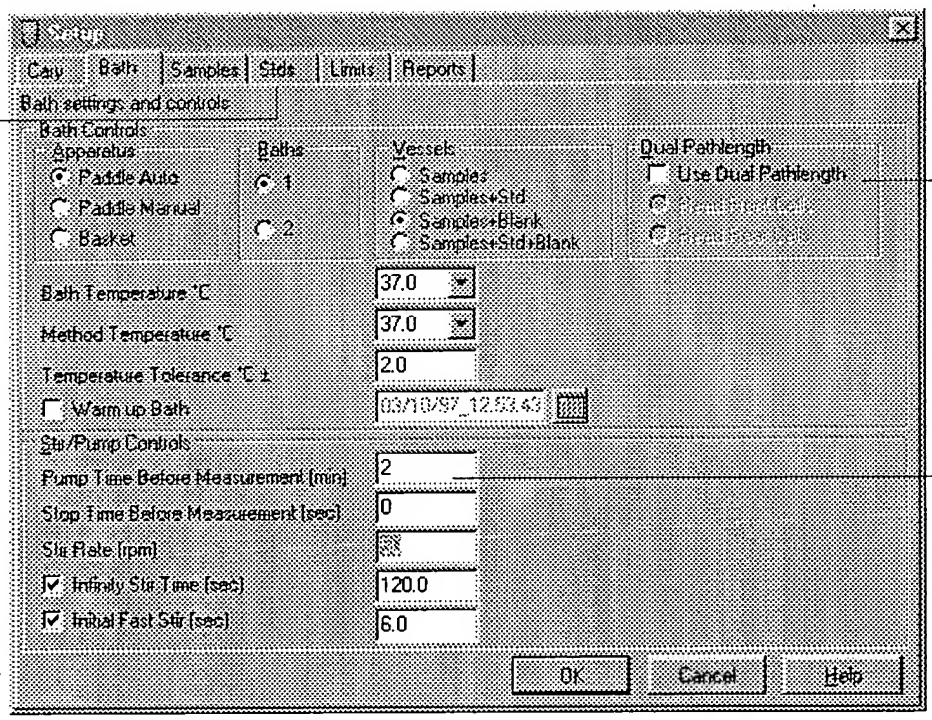
You can display any of %Dissolved vs Time, Absorbance vs Time and mg Dissolved vs Time graphics for every dissolution run.



Single or multi standard calibrations are supported, as well as a Standard Control Limits function for identification of standard measurements which are outside the specified limits during a dissolution run.

You can specify up to 3 regions in the run, each of which has a different data collection rate. This allows you to collect a lot of data when the absorbance is changing quickly and fewer data points in the more stable parts of the dissolution.

You can enter the individual tablet weights as well as the weight specified on the packaging for weight correction calculations.



With a single tester system you can set up 2 different pathlength cells and eliminate the need to change cells between runs of high and low absorption.

You can choose to pump solution just prior to a measurement, rather than continually pumping during the whole dissolution. This preserves tubing and pump lifetimes

Why do I need Cary performance?
You can measure highly absorbing samples without dilution: the extended photometric range of the Cary instruments (the Cary 100 measures up to 3.7 Abs and the Cary 300 up to 5 Abs) allows you to measure high background samples that you would normally use HPLC to measure. It also means that you can set up your measurement and walk away, confident that your samples will not be over-range when you return.

You can accurately measure sustained-release tablets: the Cary instruments are so stable you can be assured that any change in absorbance is due to the sample, not instrument drift.

Validation
Varian's quality assurance program is certified to the ISO 9001 quality standard. Varian also offers a set of compliance tools and services to simplify the validation process and to assure that you obtain quality results:

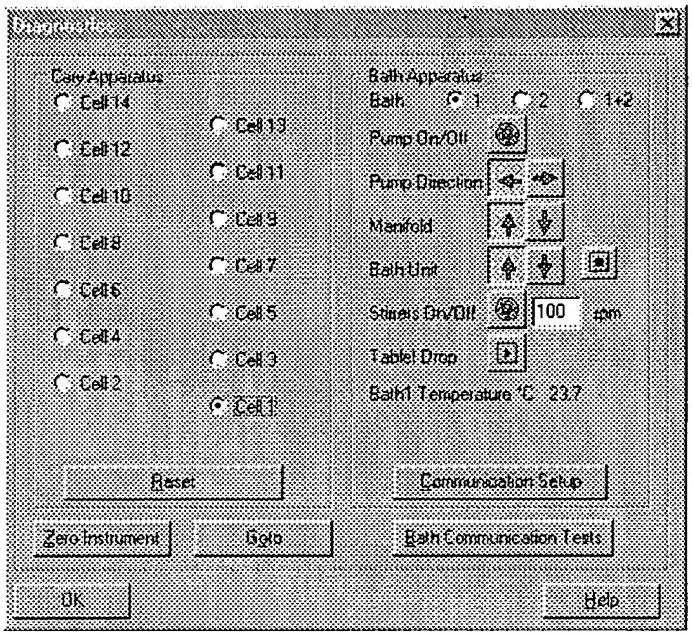
- The optional Validation documentation suite provides detailed information on the functional specification and development process of the Cary system and application software. It also contains detailed documentation to assist your initial and on-going validation activities.

- The Validate application, shipped as part of the Cary VanKel Dissolution package, provides automated testing of the Cary hardware.

- A Declaration of Conformity ships with each instrument, confirming that the instrument complies with relevant European Directives.

- System installation and qualification (optional) is performed at installation by a Varian-trained Service Representative.

- Both Varian and VanKel offer Re-certification services which can become part of your on-going Validation program. A Varian or VanKel representative will come on-site to ensure that your system is performing correctly.



A series of built-in tests can be used to test the Cary-tablet dissolution tester interface, to ensure that communications are working properly.

If any communication failure occurs during this test sequence, the system suggests actions to help correct the problem.

GLP and method integrity
A built-in Good Laboratory Practice (GLP) software package enables the laboratory administrator to specify different privileges to individuals and/or groups. For example your laboratory may consist of 2 groups of operators - Routine Operators and Method Development Operators. The Method Development Operators may have privileges allowing them to create new methods or modify existing methods. Routine Operators may only be able to load methods.

GLP and data integrity
All collected data are automatically stored during a dissolution run. The method and the report associated with the data are also stored with the data - in a single file. When data are retrieved, the method used to collect that data and the associated report are automatically retrieved ensuring that the operator can always track the way the data were collected.

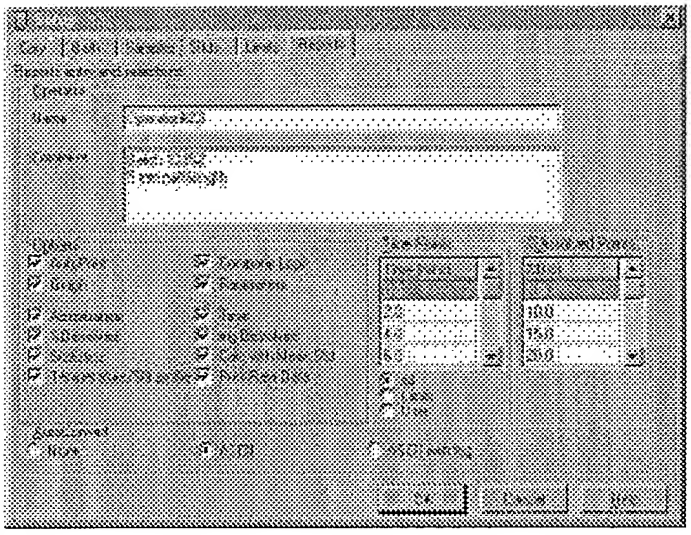
AUTOMATION AND REPORTING

How much of the system is automated?
The Cary-VanKel Tablet Dissolution system offers a very high level of automation. Each step of a dissolution run is automated.

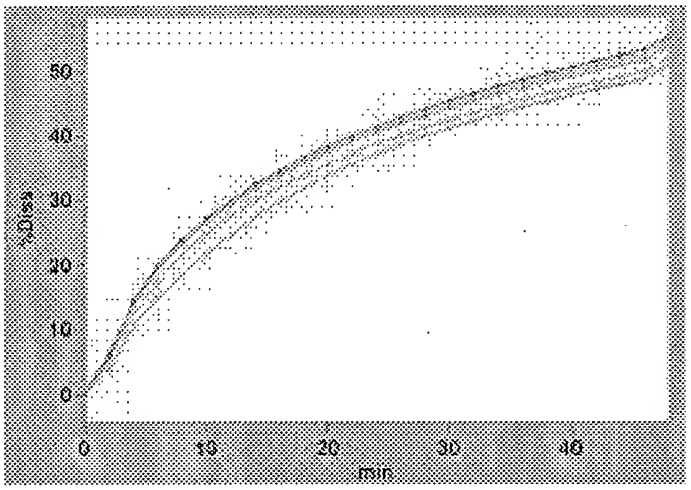
You can set and forget your dissolution run and return to pick up the report without any intervention from you.

Automatic sampling by the dissolution tester has the advantage of replacing time-consuming, tedious manual sampling as well as eliminating the errors commonly associated with manual sampling.

*optional



The reporting options are comprehensive and include GLP required information such as the operator name.
The time and date are automatically added to the report. You can also automatically convert your data for use in other soltware programs



Graphics like this can be included in a report, with each vessel being indicated by a different color trace

Glycotech
Dissolution Report

$$\%\text{Dissolved} = \frac{(\text{Sample(Abs)}-\text{Blank(Abs)})*\text{Vessel Volume(mL)}*100*\text{Standard Weight(mg)}}{(\text{Std(Abs)}-\text{Blank(Abs)})*\text{Std Flask Volume(mL)}*\text{Tablet Potency(mg)}}$$

Time (min)	Vessel 1 (%)	Vessel 2 (%)	Vessel 3 (%)	Vessel 4 (%)	Vessel 5 (%)	Vessel 6 (%)
2.0	0.6	0.7	0.6	2.1	0.3	0.3
6.0	74.6	71.7	72.4	72.8	69.2	57.5
10.0	97.0	94.6	98.1	95.0	97.0	94.1
14.0	100.2	97.8	101.3	98.3	100.7	98.7
18.0	101.3	98.8	102.3	99.4	101.9	100.1

Operator signature _____ Date _____
Supervisor signature _____ Date _____

A dissolution report can include your company logo and/or any other bitmap you like

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